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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,090	09/30/2005	Kurt Lang	20968	1980

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
09/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,090	LANG ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed May 18, 2009, is acknowledged and has been entered. Claims 10-16 have been canceled. Claims 18-21 have been newly added.

2. Claims 18-21 are pending in the application and are under examination.

Information Disclosure Statement

3. The references cited in the information disclosure statement filed on May 18, 2009, have been considered.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, Applicant's amendment and/or arguments filed May 18, 2009, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 6, 2009.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. The rejection of claims 18-21 under 35 U.S.C. 103(a) as being unpatentable over WO 00/73452 A2 (Ashkenazi et al, 2000), in view of WO 1994/22466 A1 (Cox et al, 1994, IDS filed February 2, 2006), Francis et al (Int. J. Hem., 68:1-18, 1998, IDS filed 2/2/2006), Byun et al (J. End., 169:135-143, 2001, IDS filed 2/2/2006) and Veronese et al (Biomaterials, 22:405-417, 2001, IDS filed February 2, 2006), is maintained.

Claims 18-21 are herein drawn to conjugates comprising a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and one or two branched poly(ethylene glycol) group(s), said poly(ethylene glycol) group(s) having an overall molecular weight of about 40 kDa and a composition comprising such a conjugate and a pharmaceutically acceptable carrier. Claim 19 further recites that the poly(ethylene glycol) (PEG) groups are linked to cysteine 110 and/or cysteine 117 of the polypeptide consisting of the amino acid sequence of SEQ ID NO:2. Claim 20 further recites that the poly(ethylene glycol) is bound to primary amino groups or thiol i.e., cysteine groups.

Starting at page 6 of the response filed May 18, 2009, Applicant has traversed this ground of rejection.

In this response, Applicant appears to argue that the instant claims are non-obvious because a conjugate species consisting of an IGFBP-4 polypeptide consisting

of the amino acid sequence of SEQ ID NO:2 conjugated to branched poly(ethylene glycol) group of about 40 kDa has superior properties not shown in the prior art as compared to a conjugate species consisting of an IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to a linear poly(ethylene glycol) group of about 20 kDa.

In response, this argument is not found persuasive because the arguments of counsel cannot take the place of evidence in the record. As set forth in MPEP 716.01:

> Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of ***unexpected results***, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must. be established by factual evidence." See also In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); Ex parte George, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991). The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See MPEP § 2145 generally for case law pertinent to the consideration of applicant's rebuttal arguments.

Accordingly, while the arguments of counsel that the claimed conjugates produce superior or unexpected results are noted, they were not found persuasive as no affidavit or declaration include statements regarding unexpected results has been submitted to reasonably establish the non-obviousness of the claimed conjugates. Furthermore, it is noted that the properties being referred to in the response only pertain to the properties of one species of conjugate consisting of an IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 conjugated to a single branched poly(ethylene glycol) group of about 40 kDa wherein the polypeptide is PEGylated as cysteine 110 or cysteine 117, while the pending claims encompass conjugates that are PEGylated as other sites and conjugates that are PEGylated with two branched poly(ethylene glycol) groups and no evidence or scientific reasoning has been presented to establish that any of the properties of the conjugate species taught would be shared by the other conjugate species broadly encompassed by the claims. Additionally, as set forth in the

previous office action branched PEG groups were known in the art to provide superior properties as compared to linear PEG Groups (see e.g., Veronese et al). Finally, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., increased serum half-life, more potent tumor inhibition and reduced toxicity) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Secondly, Applicant has argued that the limitation that the IGFBP-4 polypeptide is PEGylated at cysteine 110 and/or 117 distinguishes from the prior art because the prior art of Cox et al deals with introducing artificial cysteines into a protein to conjugate PEG groups to which cannot be applied to cysteine 110 and/or 117 of the IGFBP-4 polypeptide which are joined by a natural disulfide bond that is less sensitive to reduction than an artificial disulfide bond.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case, as set froth in the previous action, considering the references as a whole, one of skill in the art would have been led to PEGylate the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 by partially reducing disulfide bonds to create free thiol groups at cysteine thiol residues in the polypeptide because Byun et al teach that IGFBP-4 naturally contains 2 cysteines which form a disulfide bond in the central region that were not shown to be important for activity of the IGFBP-4 protein, and because the art recognized methods for reducing disulfide bonds to obtain free thiol groups would have been expected to work for PEGylating the IGFBP-4 polypeptide at these thiol residues. In this case, while Applicant argues that this natural disulfide bond is more stable, no evidence of this has been submitted and even if, *arguendo*, it had been presented, such evidence would not be sufficient to suggest that

the methods of the prior art of partially reducing disulfide bonds to create free thiol groups at cysteine thiol residues would not work to PEGylate this protein at cysteine 110 and/or 117 because the protein would have still have had the disulfide bond partially reduced, even if to a lesser extent. Finally, it is unclear why Applicant is arguing that the disulfide bond of cysteine 110 and 117 is highly stable, because the specification at page 11 teaches that it was assumed that this disulfide bond is highly sensitive to reduction.

Additionally, Applicant has argued that the teachings of Francis et al argues in favor of the non-obviousness of the present claims because Frances posits that there is trial and error in PEGylation of proteins.

In response, the Examiner agrees that there are more than one art known method to PEGylate polypeptides as evidenced by the references cited by the Examiner. However, the Examiner respectfully disagrees with Applicant's apparent argument that PEGylating a protein is non-obvious because one of skill in the art cannot predict the specific properties of a PEGylated protein *a priori*. In this case, as evidenced by the references as a whole, the art of PEGylating proteins had advanced so that one readily understood the advantages of PEGylating proteins, with multiple different species of PEG polymer, and in particular, a branched PEG group of about 40 kDa. Notably, as evidenced by Veronese et al in the previous office action, branched PEG groups have multiple advantages over linear PEG groups, including higher retention in blood, lower immunogenicity and decreased inactivation of the proteins activity (See page 408, Figure 5 and page 412, Figure 14) and Veronese et al further evidences that methods of conjugating a branched PEG group of about 40 kDa to proteins are known in the art (See e.g., page 408 and Figure 5[1]).

In this case, based on the references as a whole, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to PEGylate the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 with

[1] See also the Mondardini et al (Bioconj Chem, 6:62-69, 1995) reference cited by Veronese et al at page 408 which evidences that Veronese et al teach methods of PEGylating proteins with a branched PEG group of about 40 kDa

branched PEG groups of about 40 kDa because one of ordinary skill in the art readily recognized that branched PEG groups have advantages over linear PEG groups and would have had a reasonable expectation of success in making PEGylated IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 comprising branched PEG groups of about 40 kDa because the prior art taught methods of PEGylating proteins with such branched PEG groups. Notably, based on the state of the art, which provides explicit motivation to PEGylate the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and which provides art known branched PEG groups that have art recognized advantages in producing PEGylated proteins, it is maintained that one of skill in the art would have found it obvious to PEGylate the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 with branched PEG groups of about 40 kDa based on the these references as a whole.

Finally, it should further be noted that the teachings of Francis were published about three years prior to the teachings of Veronese et al, so it is submitted that the teachings of Francis are not representative of the state of the art of PEGylating proteins when considering the references as a whole.

For these reasons and as further explained in the previous Office action, as well as after careful and complete consideration of Applicant's response, this rejection is being maintained.

Conclusion

8. No claims are allowed.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent No. 6,004,775 (Shimasaki et al, 1999, of record) teaches a polypeptide that is 100% identical to SEQ ID NO: 2. US 2002/0177227 A1 (Kraus et al, 2002, of record) teach a polypeptide that is 100% identical to SEQ ID NO:2 and conjugating the polypeptides of the invention with polyethylene glycol. US Patent

No. 5,212,074 (Kiefer et al, 1993, of record) teaches a polypeptide that is 100% identical to SEQ ID NO: 2. Damon et al (Endocrinology,139:3456-3464, 1998, IDS filed February 2, 2006) teach increasing serum levels of IGFBP4 *in vivo* in a mouse prostate cancer xenograft model delays prostate tumor formation. Miyakoshi et al (Endocrinology, 142(8)3456-3464, IDS filed 02/02/2006) teach an insulin-like growth factor binding protein 4 that increases IGF bioavailability in vivo. Reddy et al (ADDR, 54:571-586, 2002, of record), teach that it is routine to optimize the PEG polymer conjugated to a polypeptide based on size and type of polymer. US Patent No. 6,207,640 (Attie et al, 2001, of record) teach methods of conjugating the proteins GH and/or IGF-I at one or two cysteine residues with monomethyl-PEG of between about 5000 Daltons to about 40000 Daltons to improve the circulating half-like for these proteins and administering such IGF-I conjugates with a IGFBP-4 polypeptide (e.g., column 13).

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935.

The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
September 4, 2009